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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/717,450	11/20/2000	Lisa Ann Neuhold	0630/D532US1	5417

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EXAMINER

WILSON, MICHAEL C

ART UNIT	PAPER NUMBER
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1632

DATE MAILED: 03/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/717,450

Applicant(s)

NEUHOLD ET AL.

Examiner

Michael C. Wilson

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 September 2003.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 55-57, 59-77 and 79-96 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 55-57, 59-77 and 79-96 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 9-9-03.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9-9-03 has been entered.

Applicant's arguments filed 9-9-03 have been fully considered but they are not persuasive. Claims 58 and 79 have been cancelled. Claims 55-57, 59-77 and 79-96 remain pending and are under consideration in the instant office action. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

The IDS filed 2-28-01 remains improper because the citations are incomplete for reasons of record. For publication purposes, proper citations are required. The abstract of DE 19501032A1 has been considered. An initialed copy of the IDS filed 9-9-03 is attached hereto.

In claim 90, "non-human transgenic mammal" in lines 2-3 should be "transgenic non-human mammal". In line 1 of step a), "transgenic mammal" should be "transgenic non-human mammal". This is to reflect the language of parent claim 55.

Claim Rejections - 35 USC § 112 – written description

Claims 55-57, 59-77 and 79-96 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The phrase "joint-specific promoter" lacks written description because the specification does not disclose any promoters that cause expression exclusively in the joint. The specification defines "joint-specific expression" as expression that is greater in joints than in other tissues; typically, the level of expression in non-joint tissues is less than 10% (pg 15, lines 19-20). Such promoters include the Type II collagen promoter (pg 16, line 3). However, the specification and the art do not teach the Type II collagen promoter causes expression greater in joints than other tissues or causes expression in non-joint tissues is less than 10%. Even if the Type II collagen promoter is "joint-specific" as defined in the specification, one species in the genus is not adequate written description of that genus. An adequate written description of a "joint-specific promoter" requires more than a mere statement that it is part of the invention. What is required is a description of a reasonable number of promoters having that function. Defining what applicants consider "joint-specific" without describing promoters having that function, as in the instant case, is simply a wish to identify promoters having that function. Naming a promoter that may exist, in the absence of knowledge as to what that material consists of, is not a description of that material. (See *Fiers v. Revel*, 25

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USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)).

It is noted that applicants argue any promoter that functions in the joint can be used in the instant invention (pg 27 of arguments). If that is the case, then the promoters are not truly "joint-specific" as claimed. In fact, the promoters of the invention are not "joint-specific" as claimed because they are not generic to any tissue of the joint. The specification does not teach bone or blood vessels of a joint can express MMP such that collagen is degraded as claimed. The specification does not teach any bone or blood vessel-specific promoters that function in the instant invention. No other "joint-specific" promoter that can express MMP and cause collagen degradation can be envisioned other than the Type II collagen promoter.

Claim Rejections - 35 USC § 112 – enablement

Claims 54-57, 59-77 and 79-96 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse whose genome comprises: a) a nucleotide sequence encoding a constitutively active, human MMP that cleaves Type II collagen, wherein the nucleotide sequence is operatively linked to a regulatable promoter; and b) a nucleotide sequence encoding a transcription activator or repressor protein operatively linked to a Type II collagen promoter, wherein expression of the metalloproteinase is capable of being repressed in the mouse until adulthood, and wherein the metalloproteinase is capable of being expressed in the mouse during adulthood to a level sufficient to cause degradation of type II collagen, does not reasonably provide enablement for any non-human mammal, or any "joint-specific promoter" as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly

connected, to make and/or use the invention commensurate in scope with these claims for reasons of record.

The claims are directed toward a transgenic non-human mammal whose genome comprises DNA encoding a constitutively enzymatically active MMP that cleaves Type II collagen in a regulatable system capable of Type II collagen degradation during adulthood, methods of degrading Type II collagen in such a mammal, and methods of evaluating compounds using such a mammal. One of the regulatory proteins is under the control of a "joint-specific promoter." The claims encompass any non-human mammal.

The state of the art at the time of filing was that it was unpredictable how to obtain the phenotype of interest in transgenics. The species-specific requirements for transgene design are not clearly understood. Examples in the literature aptly demonstrate that even closely related species carrying the same transgene construct can exhibit widely varying phenotypes. For example, several animal models of human diseases have relied on transgenic rats when the development of mouse models was not feasible. Mullins of record (1990, *Nature*, Vol. 344, pg 541-544) produced outbred Sprague-Dawley x WKY rats with hypertension caused by expression of a mouse *Ren-2* renin transgene. Hammer of record (1990, *Cell*, Vol. 63, pg 1099-1112) described spontaneous inflammatory disease in inbred Fischer and Lewis rats expressing human class I major histocompatibility allele HLA-B27 and human β_2 -microglobulin transgenes. Both investigations were preceded by the failure to develop human disease-like symptoms in transgenic mice (Mullins, 1989, *EMBO*, Vol. 8, pg 4065-4072; Taurog, 1988, *J. Immunol.*, Vol. 141, pg 4020-4023, both of record) expressing the same transgenes that successfully caused the desired symptoms in transgenic rats. Thus, the combination of elements (protein, promoter, species of protein, and species of

transgenic) required to obtain a desired phenotype were not within the realm of routine experimentation at the time of filing. The art at the time of filing also taught that attempts to engineer transgenic animals expressing MMP, e.g. MMP1 and stromelysin have not resulted in joint degeneration (pg 4, line 15, of the instant specification). As such the combination of protein, promoter, and species of transgenic required to degrade type II collagen in transgenics were unpredictable at the time the invention was made.

Not only is the difference in transgenic mice and rats unpredictable for reasons stated above, the art at the time of filing was such that a number of significant limitation regarding the production of non-mouse transgenic animals existed. Wall of record (1996, Theriogenology, Vol. 45, pg 57-68) disclosed the unpredictability of transgene behavior due to factors such as position effect and unidentified control elements resulting in a lack of transgene expression or variable expression (paragraph bridging pages 61-62). Ebert of record (1988, Mol. Endocrinology, Vol. 2, pages 277-283) taught a transgene encoding the human somatotropin gene operably linked to the mouse metallothionein promoter caused different phenotypes in transgenic pigs and mice (pg 277, col. 2, lines 17-27). Overbeek of record (1994, "Factors affecting transgenic animal production," Transgenic animal technology, pg 96-98) taught that within one litter of transgenic mice, considerable variation in the level of transgene expression occurs between founder animals and causes different phenotypes (pg 96, last para). Mullins of record (1996, J. Clin. Invest., Vol. 98, pg S37-S40) taught that non-mouse ES cells capable of providing germline chimeras were not available (pg S38, col. 1, 1st para). Therefore, it was unpredictable at the time of filing what gene of interest, promoter, enhancer, coding, or non-coding sequences present in the transgene construct, site of integration, method used and phenotype obtained were required to make a transgenic

non-human mammal of interest. The art at the time of filing did not teach any transgenic non-human mammal expressing an MMP that degrades Type II collagen or any other matrix-degrading enzyme.

The specification teaches making a transgenic mouse whose genome comprises:

- a) a nucleotide sequence encoding a constitutively active, human MMP that cleaves Type II collagen, wherein the nucleotide sequence is operatively linked to a regulatable promoter; and
- b) a nucleotide sequence encoding a transcription activator or repressor protein operatively linked to a Type II collagen promoter, wherein expression of the metalloproteinase is capable of being repressed in the mouse until adulthood, and wherein the metalloproteinase is capable of being expressed in the mouse during adulthood to a level sufficient to cause Type II collagen degradation in the joints of the mouse. Expression is controlled by the administration/withdrawal of tetracycline or other regulatory compound.

Enablement of any "joint-specific promoter"

Claims 55-57, 59-64, 66-77, 79, 81-96 are generic to any "chondrocyte-specific promoter" while claims 65 and 80 are limited to the type II collagen promoter.

The specification defines "joint-specific expression" as expression that is greater in joints than in other tissues; typically, the level of expression in non-joint tissues is less than 10% (pg 15, lines 19-20). Such promoters include the Type II collagen promoter (pg 16, line 3). However, the specification and the art do not teach the Type II collagen promoter causes expression greater in joints than other tissues or causes expression in non-joint tissues is less than 10%. Even if the Type II collagen promoter is "joint-specific" as defined in the specification, one species in the genus is not considered an enabling disclosure of that genus. An enabling disclosure of a "joint-specific promoter"

requires more than a mere statement that it is part of the invention. What is required is adequate guidance for one of skill to determine a reasonable number of promoters having that function without undue experimentation. Defining what applicants consider "joint-specific" without disclosing which promoters having that function, as in the instant case, is simply a wish to identify promoters having that function, and leaves the persons of skill with undue experimentation. Therefore, the phrase "joint-specific promoter" is not enabled.

Again, applicants argue any promoter that functions in the joint can be used in the instant invention (pg 29 of arguments, 2nd full ¶). If that is the case, then the promoters used in the invention are not truly "joint-specific" as claimed. In fact, the promoters of the invention are not "joint-specific" as claimed because they are not generic to any tissue of the joint. The specification does not describe expressing MMP in any joint tissue other than chondrocytes. For example, the specification does not teach bone or blood vessels of a joint of the mouse claimed can express MMP such that collagen is degraded as claimed. The specification does not teach any bone, blood vessel or other joint-specific promoters that function in the instant invention. Applicants' reiterate previous arguments and point to other applications and other promoters, none of which would cause expression in the joint of the animal of the invention as required in the instant invention. No other "joint-specific" promoter that can express MMP and cause collagen degradation can be envisioned in the invention other than the Type II collagen promoter.

Enablement of any "transgenic non-human mammal"

Claims 55-57, 59-63, 67-71, 75-77, 79-91 and 93-96 are generic to any transgenic non-human mammal while claims 64-66 are limited to a transgenic rat.

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Given the unpredictability of phenotypes between mice and rats taken with the unpredictability regarding obtaining transgenics other than mice, the unpredictability regarding the parameters required to obtain a phenotype of interest in transgenics and the lack of guidance provided in the specification regarding how to obtain transgenics other than mice and the lack of guidance provided in the specification regarding how to obtain Type II collagen degradation in mammals other than mice and the lack of correlation in the specification regarding how to obtain the phenotype found in mice in other mammalian species, the specification does not enable making any transgenic non-human mammal capable of degrading Type II collagen as claimed other than mice.

Applicants argue Cameron does not support the Examiner's assertion because Cameron does not correlate diversity of chromatin structure with species-specificity. Applicants argue Cameron supports the Applicants' assertion that it was routine to screen for transgenics that work. Applicants' arguments are not persuasive. Cameron clearly taught that the genetic diversity of different species of mice added to the unpredictability of the phenotype caused by a transgene. Cameron (1997, Molec. Biol., Vol. 7, pg 253-265) taught expression of a transgene was unpredictable because of the insertion site of the transgene into the genome and the surrounding genetic background. Predictable levels of expression are not achieved because of the complete absence of expression or leaky expression in non-target tissues (pg 256, ¶ bridging col. 1-2). Factors causing variable expression, or the lack thereof, are not affected by copy number and such effects are seen in lines of transgenic mice made with the same construct (pg 256, col. 2, lines 3-9). These factors are copy number independent and

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integration site dependent, emphasizing the role the genetic background and site of integration in the level of expression of the transgene (pg 256, lines 10-13). Thus, different strains of mice having the same transgene have different phenotypes. Increased genetic diversity caused increased, unpredictable differences in phenotype.

Applicants do not teach how to achieve the phenotype described in any species other than mice. Applicants do not correlate the phenotype obtained in mice to any other species. Applicants do not teach how to overcome the genetic diversity of other species so that "joint-specific" MMP expression occurs in other species. Merely screening animals of other species for the desired expression pattern or phenotype is not the issue. The issues are whether the amount of MMP expression, the "joint-specificity" of MMP expression or the desired phenotype will occur in other species because, in fact, the desired parameters may never occur in other species. The specification does provide adequate guidance that the Type II collagen promoter described in the specification will function as desired in other species or that the desired phenotype does occur in species other than mice. Given the unpredictability in the art taken with the mere statement in the specification that other species are encompassed by the invention, it would require one of skill undue experimentation to obtain the desired phenotype in species other than mice because the desired animal may never be obtained in other species.

Applicants reiterate the arguments regarding the second declaration of Dr. Neuhold (Exhibit 5, para. 9), which was discussed in the last office action. The response was as follows:

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The declaration states generating transgenic animals having the desired feature was routine at the time of filing. The declaration refers to Bradley (1996, Nature Genetics, Vol. 14, pg 121) who states

"For almost 15 years the methods for making transgenic mammals have remained virtually unchanged, consisting of the injection of naked DNA into the pronucleus of a fertilized egg. The technique is so reliable that the technical shortcomings can readily be circumvented by producing an excess of experimental material so that animals with the desired experimental outcome can be selected from a collection of founder mice¹."

1. Palmiter (1985, Cell, Vol. 41, pg343-345).

Dr. Neuhold concludes para. 9 by stating that as of 1996, creation of transgenic mammals required no more than ordinary technical effects (para. 9).

Applicants' arguments are not persuasive.

Bradley (1996) taught animals with the "desired experimental outcome" can be selected from a collection of founder mice. In context, Bradley (1996) merely discusses the ability to screen a collection of founder transgenics to determine founders that carried the transgene of interest. Bradley did not teach screening founder mice predictably resulted in identifying animals with the desired phenotype. Bradley did not teach how to make any mammals other than mice (see the citation at the end of the first sentence of Bradley, i.e. Palmiter, which only taught making transgenic mice). Bradley did not teach making non-mouse transgenics was routine. Bradley did not teach the phenotype obtained in transgenic mice predictably occurs in other mammals. The art taught phenotypes in mice do not occur in rats using the same construct (Mullins (1990), Hammer (1990), Mullins (1989), Taurog (1988) all of record). Mullins of record

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(1996, J. Clin. Invest. Vol. 98, pg S37-S40) taught transgene constructs react very differently from one species to another (pg S38, col. 1, last para.). Mullins (1993, Hypertension, Vol. 22, pp. 630-633) taught integration of a transgene into different species of animal gave divergent phenotypes. Ebert of record (1988, Mol. Endocrinology, Vol. 2, pages 277-283) taught a transgene encoding the human somatotropin gene operably linked to the mouse metallothionein promoter caused different phenotypes in transgenic pigs and mice (page 277, column 2, lines 17-27). Wall of record (1996, Theriogenology, Vol. 45, pages 57-68) taught the physiological result of transgene expression in livestock was not predicted in transgenic mice (page 62, line 7). Therefore, the mere ability to make and screen transgenics that carry the transgene construct is not adequate for one of skill to predictably obtain the phenotype in mice in other mammalian species.

Dr. Neuhold states in paragraph 10 that the elements used in the mouse disclosed could be used in non-mouse species and "the only uncertainty remaining was to establish that this combination of features would cause phenotypic changes of osteoarthritis in a transgenic animal" (¶ 10) which are described in the specification and could easily be screened for. Dr. Neuhold states in paragraph 11 that by teaching the combination of elements used to obtain the phenotype of interest in mice, there is a more than reasonable expectation of obtaining any transgenic mammal which will work better.

Applicants' arguments are not persuasive. The specification, the declaration of Dr. Neuhold and Bradley (1996) do not adequately correlate the elements used in the

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disclosed mouse to other mammals such that the phenotype obtained in mice could be obtained in other mammals. The specification does not teach the level of expression of MMP and expression of the regulatory protein obtained in mice would be the same in other mammals using the same construct. The specification does not teach the Type II collagen promoter causes the same level of protein expression in mice and other mammals. The specification does not teach MMP degrades collagen to the same extent in mice and other mammals. The specification does not teach MMP causes the same level of Type II collagen degradation cause the symptoms claimed in mice and other mammals. The specification does not teach the level of regulatory protein expressed that regulates MMP expression in mice is the same level required in other species. Without such guidance, taken with the unpredictability in the art, one of skill could not predict whether the phenotype in mice would occur in other species. Mere screening for a phenotype of interest would not allow one of skill in the art to predict whether the phenotype would occur in species other than mice.

Claim Rejections - 35 USC § 112 – indefiniteness

Claims 90-96 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 90-96 remain indefinite because the "control transgenic mammal in which the composition was not administered by expression of the metalloproteinase was activated" is unclear. The claims do not clearly set forth that the control animal has the same genome as the animal of step a) or that the control animal has had MMP

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activated, collagen degradation or one of the phenotypes listed in a). One way to overcome this rejection is to start the claim by --providing a first and second non-human transgenic mammal...-- followed by "administering a compound to the first transgenic non-human mammal but not the second transgenic non-human mammal" and "comparing the phenotype of the first and second transgenic non-human mammal, wherein...".

Finally, the test required to determine compounds of interest in claims 90-96 are not clearly set forth. Use of the phrase "phenotypic change" is inaccurate because the phenotype does not change. One phenotype is compared to another.

The claims are free of the prior art of record.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at 571-272-0738.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached on 571-272-0804.

The official fax number for this Group is (703) 872-9306.

Michael C. Wilson



**MICHAEL WILSON
PRIMARY EXAMINER**